

**FAX TRANSMISSION SHEET**

DATE: April 15, 2003

TO: Examiner Liu, Hong

FAX: 703.746.5122

TEL: 703.306.5814

BOSTON

CC:

FAX:

TEL:

BRUSSELS

FROM: Arthur E. Jackson, Ph.D.

FAX: 609.620.3259

TEL: 609.620.3254

ROOM:

EMAIL: Arthur.Jackson@dechert.com

FRANKFURT

CLIENT: 361331-512

MATTER: 301200

HARRISBURG

**TOTAL PAGES (INCLUDING COVER SHEET): 6**

HARTFORD

**CONFIDENTIALITY NOTE:** The information contained in this facsimile message is legally privileged and confidential information intended only for the use of the individual or entity named above. If you are not the intended recipient, you are hereby notified that you should not further disseminate, distribute or copy this message. In addition, if you have received this message in error, please notify us immediately by collect telephone call and return the original message to us at the address below via the United States Postal Service. Thank you.

LONDON

LUXEMBOURG

**MESSAGE**

NEW YORK

Re: 10/036,857

Elected Compounds

NEWPORT BEACH

149571.1.07

PARIS

PHILADELPHIA

PRINCETON

SAN FRANCISCO

WASHINGTON

**IF ALL PAGES ARE NOT RECEIVED, PLEASE CALL 609.620.3204**

Law Offices of Dechert LLP  
A Pennsylvania Limited Liability Partnership

James J. Marino • Resident Managing Partner

Princeton Pik Corporate Center • P.O. Box 5218 • Princeton, NJ 08543-5218

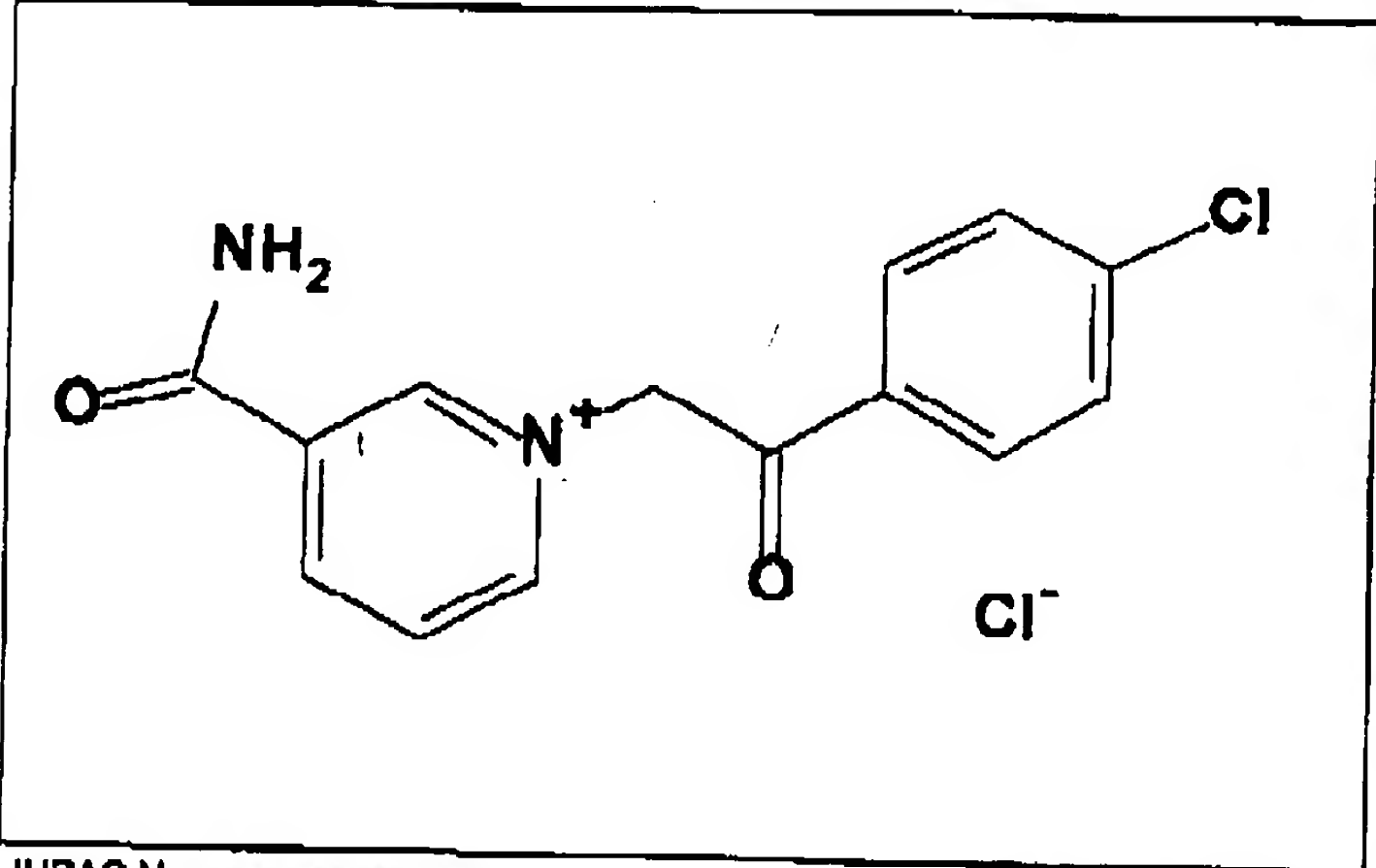
Tel: 609.620.3200 • Fax: 609.620.3259 • www.dechert.com

Delivery Address: 997 Lenox Dr., Bldg. 3, Ste. 210 • Lawrenceville, NJ 08648

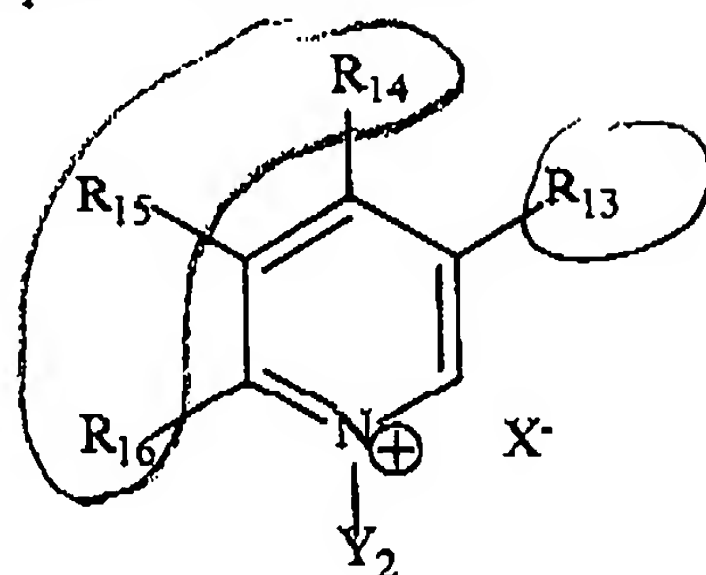
Attention Ex Liu, Hong  
No 10/036,857

703-746-5122 fx  
703-306-5814 ph

Elected compound

	Formula	
	C <sub>14</sub> H <sub>12</sub> Cl <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	
	Mol. Wt.	ClogP
	311.167	-1.5154
	Chemist	
M. Pagan		
Quantity	MP	
	284-285C	
IUPAC Name		
3-Carbamoyl-1-[2-(4-chloro-phenyl)-2-oxo-ethyl]-pyridinium; chloride		
Solubility		
Alcohols, Water and DMSO		

28. A compound of formula VI:



(VII)

wherein  
a. R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup>

1. are independently selected from (hydrogen), acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxy carbonyl, alkoxy carbonylalkyl, alkyl, alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, Ar<sup>3</sup> (wherein Ar<sup>3</sup> is C<sub>6</sub> or C<sub>10</sub> aryl), Ar<sup>3</sup>-alkyl, Ar<sup>3</sup>-O, Ar<sup>3</sup>SO<sub>2</sub>-, Ar<sup>3</sup>SO-, Ar<sup>3</sup>S-, Ar<sup>3</sup>SO<sub>2</sub>NH-, Ar<sup>3</sup>NH-, (N-Ar<sup>3</sup>)(N-alkyl)N-, Ar<sup>3</sup>C(O)-, Ar<sup>3</sup>C(O)NH-, Ar<sup>3</sup>NH-C(O)-, and (N-Ar<sup>3</sup>)(N-alkyl)N-C(O)-, or together R<sub>1</sub> and R<sub>2</sub> comprise methylenedioxy; or
2. form, with an adjacent pair from R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup>, together with their ring carbons, a C<sub>6</sub>- or C<sub>10</sub>- aromatic fused ring system; or
3. form, with an adjacent pair from R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup>, together with their ring carbons, a C<sub>5</sub>-C<sub>7</sub> fused cycloalkyl ring having up to two double bonds including the fused double bond of the pyridinium containing ring, which cycloalkyl ring can be substituted by one or more of the group consisting of alkyl, alkoxy carbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. form, with an adjacent pair from R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup>, together with their ring carbons, a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring may be optionally substituted with one or more 1-pyrrolidinyl-, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl,

10

wherein R<sub>s</sub> is a [C<sub>6</sub> or C<sub>10</sub>]aryl or a heterocycle containing 4-10

ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur, or

or R<sub>s</sub>,

azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups; or

5. form, with an adjacent pair from R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup> and R<sup>16</sup>, together with their ring carbons, a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and S(O)<sub>n</sub>, where n=0,1, or 2;

b. Y<sup>2</sup> is a group of the formula -CH(R<sup>5</sup>)-R<sup>6</sup> wherein

(a) R<sup>5</sup> is hydrogen, alkyl-, cycloalkyl-, alkenyl-, alkynyl-, aminoalkyl-, dialkylaminoalkyl-, (N-[C<sub>6</sub> or C<sub>10</sub>]aryl)(N-alkyl)aminoalkyl-, piperidin-1-ylalkyl-, 1-pyrrolidin-1-ylalkyl, azetidinyalkyl, 4-alkylpiperazin-1-ylalkyl, 4-alkylpiperidin-1-ylalkyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-ylalkyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-ylalkyl, azetidin-1-ylalkyl, morpholin-4-ylalkyl, thiomorpholin-4-ylalkyl, piperidin-1-ylalkyl, [C<sub>6</sub> or C<sub>10</sub>]aryl, or independently the same as R<sup>6</sup>;

(b) R<sup>6</sup> is phenyl substituted at the para position with chloro or fluoro;

(2) a group of the formula -W-R<sub>s</sub>, wherein W is C(=O)- or -S(O)<sub>n</sub>- where n=1 or 2;

(3) a group of the formula -W-N(R<sup>9</sup>)R<sup>10</sup>, wherein

[a] R<sup>9</sup> is hydrogen and R<sup>10</sup> is an alkyl or cycloalkyl, optionally substituted by

(i) [C<sub>6</sub> or C<sub>10</sub>]aryl, or

(ii) a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, said heteroaryl ring can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, and morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy groups, or fused to a phenyl or pyridine ring, wherein the ring fusion is at a carbon-carbon double bond of the heteroaryl ring, or

(iii) a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur; or

[b] R<sup>9</sup> is hydrogen or lower alkyl and R<sup>10</sup> is Ar<sup>3</sup>; or

- [c] R<sup>9</sup> is hydrogen or lower alkyl, and R<sup>10</sup> is a heterocycle containing 4-10 ring atoms of which 1-3 are heteroatoms are selected from the group consisting of oxygen, nitrogen and sulfur, said heterocycle; or
- [d] R<sup>9</sup> and R<sup>10</sup> are both alkyl groups; or
- 5 [e] R<sup>9</sup> and R<sup>10</sup> together with N form a heterocycle containing 4-10 ring atoms which can incorporate up to one additional heteroatom selected from the group of N, O or S in the ring, wherein the heterocycle is optionally substituted with (C<sub>6</sub>-or C<sub>10</sub>)aryl, (C<sub>6</sub>-or C<sub>10</sub>)arylalkyl, or a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and
- 10 zero to two atoms of N, each such heteroaryl can be optionally substituted with one or more 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C<sub>1</sub>-
- 15 C<sub>3</sub>)alkylenedioxy; or
- [f] R<sup>9</sup> and R<sup>10</sup> are both hydrogen;
- c. X is a pharmaceutically acceptable anion, or
- (B) a pharmaceutically acceptable salt of the compound,
- 20 wherein (aryl) or Ar<sup>3</sup> can be substituted with, in addition to any substitutions specifically noted, one or more general substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C<sub>1</sub>-C<sub>3</sub>)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino,
- 25 Ar<sup>3</sup>C(O)-, Ar<sup>3</sup>C(O)NH-, Ar<sup>3</sup>O-, Ar<sup>3</sup>-, Ar<sup>3</sup>-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, (halo) trifluoromethyl, hydroxy, (C<sub>2</sub>-C<sub>6</sub>)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperazin-1-yl-, 4-[C<sub>6</sub> or C<sub>10</sub>]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl;
- 30 wherein heterocycles, except those of Ar<sup>3</sup>, can be substituted with, in addition to any substitutions specifically noted, the following general substitutions: acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, Ar<sup>3</sup>C(O)-, Ar<sup>3</sup>O-, Ar<sup>3</sup>-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or
- 35 trifluoromethyl;

wherein, if the compound of formula VII has a core structure comprising a pyridinium ring having a 2-aryl-2-oxoethyl substitution at the 1 position, wherein the aryl can be substituted, and a formyl which may be substituted at the 3 position, one or both of the following applies:

- 5           the compound of formula VII differs from a salt of pyridinium compound having a 1-(2-aryl-2-oxoethyl), wherein the aryl can be substituted, and a formyl which may be substituted at the 3 position by at least one additional substitution at  $R^{14}$ ,  $R^{15}$  or  $R^{16}$ , or the aryl of 2-aryl-2-oxoethyl is phenyl and is substituted at the para  
10           position with an electron withdrawing group selected from fluoro, chloro, nitro, trifluoromethyl, and carbamoyl; and

wherein the compound of formula VII differs from a salt of 1-[2-(4-methylphenyl)-2-oxoethyl]-pyridinium by one or more of the lack or replacement of the methyl substitution, or the presence of one or more additional substitutions.

15